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Chem-Bio News – S&T Edition

1. BIOMARKERS OF ORGANOPHOSPHORUS NERVE AGENT EXPOSURE: COMPARISON OF PHOSPHYLATED BUTYRYLCHOLINESTERASE AND PHOSPHYLATED ALBUMIN AFTER OXIME THERAPY: *"No BuChE adducts were detected in animals exposed to sarin and cyclosarin where samples were collected only after 23 or 24 days."*

2. NEW ORNL[OAK RIDGE NATIONAL LABORATORY] SENSOR EXPLOITS TRADITIONAL WEAKNESS OF NANO DEVICES: *"Ultimately, researchers believe this new "sniffer" will achieve a detection level that approaches the theoretical limit, surpassing other state-of-the-art chemical sensors."*

3. A GENOME-WIDE SCREEN IN SACCHAROMYCES CEREVISIAE REVEALS A CRITICAL ROLE FOR THE MITOCHONDRIA IN THE TOXICITY OF A TRICHOHECENE MYCOTOXIN: *"These results provide genome-wide insight into the mode of action of trichothecene mycotoxins and uncover a critical role for mitochondrial translation and membrane maintenance in their toxicity."*

4. BIOCOMPATIBLE ELECTROCHEMILUMINESCENT BIOSENSOR FOR CHOLINE BASED ON ENZYME/TITANATE NANOTUBES/CHITOSAN COMPOSITE MODIFIED ELECTRODE: *"The work would provide a common platform to develop various sensitive, selective and biocompatible ECL biosensors based on using enzyme/TNTs/CHIT composite films."*

5. ANTHRAX LETTERS: PERSONAL EXPOSURE, BUILDING CONTAMINATION, AND EFFECTIVENESS OF IMMEDIATE MITIGATION MEASURES: *"Results demonstrated that the spore aerosol spread throughout the building in less than 4.5 min. Potential mitigation techniques such as closing the office door or shutting off the ventilation system were not effective."*

6. RAPID SIMULTANEOUS DETERMINATION OF APOPTOSIS, NECROSIS, AND VIABILITY IN SULFUR MUSTARD EXPOSED HACAT CELL CULTURES: *"This assay is highly effective in quantifying apoptosis and necrosis caused by cytotoxic agents and in estimating protective effects of potential active pharmaceutical ingredients."*

7. QUANTITATIVE ANTI-F1 AND ANTI-V IGG ELISAS AS SEROLOGICAL CORRELATES OF PROTECTION AGAINST PLAGUE IN FEMALE SWISS WEBSTER

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CB Daily Report

Chem-Bio News

BIOMARKERS OF ORGANOPHOSPHORUS NERVE AGENT EXPOSURE: COMPARISON OF PHOSPHYLATED BUTYRYLCHOLINESTERASE AND PHOSPHYLATED ALBUMIN AFTER OXIME THERAPY

Pharma Law Weekly
February 23, 2010

"Organophosphorus nerve agents inhibit the activity of cholinesterases by phosphorylation of the active site serine. In addition, sarin, cyclosarin, soman and tabun have been shown to phosphorylate a tyrosine residue in albumin."

"Therapies against nerve agent poisoning include the use of oximes to reactivate inhibited cholinesterases by displacement of the phosphyl moiety and hence detectable levels of adducts with cholinesterases may be reduced. Adducts with tyrosine have been shown to be persistent in the guinea pig in the presence of oxime therapy. Plasma samples obtained from an animal study aimed at improving therapy against nerve agent poisoning were used to compare the suitability of tyrosine and butyrylcholinesterase (BuChE) adducts as biomarkers of nerve agent exposure after treatment with therapeutic oximes. Under the terms of the project licence, these samples could be collected only on death of the animal, which occurred within hours of exposure or when culled at 23 or 24 days. Tyrosine adducts were detected in all samples collected following intra-muscular administration of twice the LD50 dose of the respective nerve agent. Aged BuChE adducts were detected in samples collected within a few hours after administration of soman and tabun, but not after 23 or 24 days."

"No BuChE adducts were detected in animals exposed to sarin and cyclosarin where samples were collected only after 23 or 24 days."

The full article can be found at: (R.W. Read, et. al., "Biomarkers of organophosphorus nerve agent exposure: comparison of phosphylated butyrylcholinesterase and phosphylated albumin after oxime therapy". Archives of Toxicology, 2010;84(1):25-36). Link not available.

NEW ORNL [OAK RIDGE NATIONAL LABORATORY] SENSOR EXPLOITS TRADITIONAL WEAKNESS OF NANO DEVICES

Oak Ridge National Laboratory News Release

February 12, 2010

"By taking advantage of a phenomenon that until now has been a virtual showstopper for electronics designers, a team led by Oak Ridge National Laboratory's Panos Datskos is developing a chemical and biological sensor with unprecedented sensitivity.

Ultimately, researchers believe this new "sniffer" will achieve a detection level that approaches the theoretical limit, surpassing other state-of-the-art chemical sensors. The implications could be significant for anyone whose job is to detect explosives, biological agents and narcotics.

"While the research community has been avoiding the nonlinearity associated with the nanoscale mechanical oscillators, we are embracing it," said co-developer Nickolay Lavrik, a member of the Department of Energy lab's Center for Nanophase Materials Sciences Division. "In the end, we hope to have a device capable of detecting incredibly small amounts of explosives compared to today's chemical sensors."

The device consists of a digital camera, a laser, imaging optics, a signal generator, digital signal processing and other components that collectively, much like a dog's nose, can detect tiny amounts of substances in the air.

The underlying concept is based on micro-scale resonators that are similar to microcantilevers used in atomic force microscopy, which has recently been explored as mass and force sensing devices. Although the basic principle is simple - measuring changes in the resonance frequency due to mass changes - a number of obstacles have impeded widespread applications of such systems.

"These challenges are due to requirements of measuring and analyzing tiny oscillation amplitudes that are about the size of a hydrogen atom," Lavrik said. Such traditional approaches require sophisticated low-noise electronic components such as lock-in amplifiers and phase-locked loops, which add cost and complexity.

Instead, this new type of sniffer works by deliberately hitting the microcantilevers with relatively large amounts of energy associated with a range of frequencies, forcing them into wide oscillation, or movement. Lavrik likened the response to a diving board's movement after a swimmer dives.

"In the past, people wanted to avoid this high amplitude because of the high distortion associated with that type of response," said Datskos, a member of the Measurement Science and Systems Engineering Division. "But now we can exploit that response by tuning the system to a very specific frequency that is associated with the specific chemical or compound we want to detect."

When the target chemical reacts with the microcantilever, it shifts the frequency depending on the weight of the compound, thereby providing the detection.

"With this new approach, when the microcantilever stops oscillating we know with high certainty that the target chemical or compound is present," Lavrik said.

The researchers envision this technology being incorporated in a handheld instrument that could be used by transportation security screeners, law enforcement officials and the military. Other potential applications are in biomedicine, environmental science, homeland security and analytical chemistry.

With adequate levels of funding, Datskos envisions a prototype being developed within six to 18 months."

The full article can be found at: http://www.ornl.gov/info/press_releases/get_press_release.cfm?ReleaseNumber=mr20100212-01

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A GENOME-WIDE SCREEN IN SACCHAROMYCES CEREVISIAE REVEALS A CRITICAL ROLE FOR THE MITOCHONDRIA IN THE TOXICITY OF A TRICHOHECENE MYCOTOXIN

Science Letter

February 23, 2010

"Trichothecene mycotoxins synthesized by *Fusarium* species are potent inhibitors of eukaryotic translation. They are encountered in both the environment and in food, posing a threat to human and animal health."

"They have diverse roles in the cell that are not limited to the inhibition of protein synthesis. To understand the trichothecene mechanism of action, we screened the yeast knockout library to identify genes whose deletion confers resistance to trichothecin (Tcin). The largest group of resistant strains affected mitochondrial function, suggesting a role for fully active mitochondria in trichothecene toxicity. Tcin inhibited mitochondrial translation in the wild-type strain to a greater extent than in the most resistant strains, implicating mitochondrial translation as a previously unrecognized site of action. The Tcin-resistant strains were cross-resistant to anisomycin and chloramphenicol, suggesting that Tcin targets the peptidyltransferase center of mitochondrial ribosomes. Tcin-induced cell death was partially rescued by mutants that regulate mitochondrial fusion and maintenance of the tubular morphology of mitochondria. Treatment of yeast cells with Tcin led to the fragmentation of the tubular mitochondrial network, supporting a role for Tcin in disruption of mitochondrial membrane morphology."

"These results provide genome-wide insight into the mode of action of trichothecene mycotoxins and uncover a critical role for mitochondrial translation and membrane

maintenance in their toxicity."

The full article can be found at: (J.E. Mclaughlin, et. al., "A genome-wide screen in *Saccharomyces cerevisiae* reveals a critical role for the mitochondria in the toxicity of a trichothecene mycotoxin". Proceedings of the National Academy of Sciences of the United States of America, 2009; 106(51):21883-21888). Link not available.

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BIOCOMPATIBLE ELECTROCHEMILUMINESCENT BIOSENSOR FOR CHOLINE BASED ON ENZYME/TITANATE NANOTUBES/CHITOSAN COMPOSITE MODIFIED ELECTRODE

Medicine & Law Weekly
February 26, 2010

"A new biocompatible ECL biosensor based on enzyme/titanate nanotubes/chitosan composite film was developed for the determination of analytes in biological samples. In the fabrication of the new ECL biosensor, biocompatible titanate nanotubes (TNTs) and a model enzyme, i.e., choline oxidase (ChOX), were immobilized on a chitosan modified glassy carbon electrode (GCE) via electrostatic adsorption and covalent interaction, respectively."

"By this ECL biosensor, choline was enzymatically oxidized to hydrogen peroxide and detected by a sensitive luminol ECL system. The use of TNTs not only provided a biocompatible microenvironment for the immobilized enzyme, which resulted in an excellent stability and long lifetime of the ECL biosensor, but also exhibited great enhancement towards luminol ECL and thus led to a significant improvement in sensitivity of ECL biosensor. Satisfactory results were obtained when employing this biosensor in assaying the total choline in milk samples."

"The work would provide a common platform to develop various sensitive, selective and biocompatible ECL biosensors based on using enzyme/TNTs/CHIT composite films."

The full article can be found at: (H. Dai, et. al., "Biocompatible electrochemiluminescent biosensor for choline based on enzyme/titanate nanotubes/chitosan composite modified electrode". Biosensors & Bioelectronics, 2010; 25(6): 1414-9). Link not available.

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ANTHRAX LETTERS: PERSONAL EXPOSURE, BUILDING CONTAMINATION, AND EFFECTIVENESS OF IMMEDIATE MITIGATION MEASURES

Preventive Medicine Week
February 21, 2010

"This report is the first detailed and quantitative study of potential mitigation procedures intended to deal with anthrax letters using a simulated anthrax letter release within an

actual office building. Spore aerosols were created by opening letters containing 0.1 g of dry powdered *Bacillus atrophaeus* spores."

"Culturable aerosol samples were collected using slit-to-agar and filter-based samplers. Five test scenarios were designed to determine whether simple mitigation procedures or activities carried out by the person who opened the letter made a significant difference to aerosol concentrations in comparison to a control scenario where no activity took place. Surface contamination of the letter opener was measured at 10 body points for Scenarios 1 to 4. A sixth scenario, based on published Centers for Disease Control and Prevention anthrax letter response guidelines, used letters containing 1 g of spores. Results demonstrated that the spore aerosol spread throughout the building in less than 4.5 min. Potential mitigation techniques such as closing the office door or shutting off the ventilation system were not effective. Activities carried out by the letter opener including moving, walking to another location, and spraying water onto the contaminated desk with a hand sprayer all resulted in significantly higher aerosol concentrations in comparison to control. The potential total inhalational hazard for the letter opener during the five test scenarios ranged from 4.1×10^5 to 1.6×10^6 colony forming units (CFU) compared to 3.9×10^5 CFU for the control. Surface contamination of the letter opener (Scenarios 1 to 4) was highest on the right hip (4.8×10^4 to 1.0×10^5 CFU/cm²) and lowest on the right or left side of the head (2.2×10^2 to 3.7×10^3 CFU/cm²). The statistically based methodology used in this study provided the means to objectively assess anthrax letter protocols to determine their effectiveness under realistic conditions."

"Potential mitigation procedures tested in this study did not reduce aerosol hazard or surface contamination."

The full article can be found at: (B. Kournikakis, et. al., "Anthrax letters: personal exposure, building contamination, and effectiveness of immediate mitigation measures". *Journal of Occupational and Environmental Hygiene*, 2010; 7(2):71-9). Link not available.

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RAPID SIMULTANEOUS DETERMINATION OF APOPTOSIS, NECROSIS, AND VIABILITY IN SULFUR MUSTARD EXPOSED HACAT CELL CULTURES

Pharma Law Weekly
February 16, 2010

"Sulfur mustard (SM; bis(2-chloroethyl)sulphide; HD) is a blister inducing agent causing DNA damage and subsequently, cell death, mostly by apoptosis in basal keratinocytes. Despite intensive investigations on the cellular mechanism, there are, as of now, no causal therapeutics to prevent or antagonize SM-related damage to cells and tissues."

"In order to develop treatment strategies against vesication, it is important to distinguish apoptosis from necrosis in SM treated human keratinocytes. DNA fragmentation is a hallmark of apoptosis and regulated by a cascade of enzymes (endonucleases, DNase1, NUC 18), which finally cut the chromatin into specific formations of 180-200 base pairs, the nucleosomes. A feasible way to monitor apoptosis is the detection of nucleosomes by means

of the Cell Death Detection ELISA(plus)[®] (CDDE) In contrast, during necrosis DNA fragmentation is at random and delivers larger fragments, which therefore are significantly less in number and predominantly occur in cell culture supernatant. To monitor necrosis, we measured the release of intracellular adenylate kinase (AK) into cell culture supernatant by means of the ToxiLight[®] Bioluminescence Assay (TL). With combination of the Cell Death Detection ELISA(plus)[®] and the ToxiLight[®] Bioluminescence Assay, we acquired more comprehensive information on cell survival and mechanisms of cell death, following an SM exposure. To validate the assay we tested common apoptosis- and necrosis-inducing agents like SM 300 mc M for 30 min, Lewisite (L) 60 mc M for 5 min and Triton X-100 0.1%. The results show that it is possible to differentiate between the two modes of cell death and to quantify their extent."

"This assay is highly effective in quantifying apoptosis and necrosis caused by cytotoxic agents and in estimating protective effects of potential active pharmaceutical ingredients."

The full article can be found at: (A. Heinrich, et. al., "Rapid simultaneous determination of apoptosis, necrosis, and viability in sulfur mustard exposed HaCaT cell cultures". Toxicology Letters, 2009;191(2-3):260-267). Link not available.

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QUANTITATIVE ANTI-F1 AND ANTI-V IGG ELISAS AS SEROLOGICAL CORRELATES OF PROTECTION AGAINST PLAGUE IN FEMALE SWISS WEBSTER MICE

Health Risk Factor Week

February 23, 2010

"A recombinant fusion protein composed of Yersinia pestis fraction 1 capsule (F1) and virulence-associated V antigen (V) (F1-V) has been developed as the next-generation vaccine against plague."

"In this study, female Swiss Webster mice received a single intramuscular vaccination with one of eight doses of the F1-V vaccine and exposed 4 weeks later to either Y. pestis CO92 or C12 organisms by the subcutaneous or aerosol routes of infection. Quantitative anti-F1 and anti-V immunoglobulin G (IgG) ELISAs were used to examine the relationship between survival outcome and antibody titers to F1 and V."

"Results suggested that each 1log(10) increase in week 4 quantitative anti-F1 and anti-V IgG ELISA titers were associated with a 1.7-fold (p=0.0051) and 2.5-fold (p=0.0054) increase in odds of survival, respectively, against either bubonic or pneumonic plague and may serve as serological correlates of protection."

The full article can be found at: (S.F. Little, et. al., "Quantitative anti-F1 and anti-V IgG ELISAs as serological correlates of protection against plague in female Swiss Webster mice". Vaccine, 2010;28(4):934-9). Link not available.

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INCREASED SERUM FERRITIN LEVELS IN PATIENTS WITH CRIMEAN-CONGO HEMORRHAGIC FEVER: CAN IT BE A NEW SEVERITY CRITERION?

World Disease Weekly
February 23, 2010

"Serum ferritin is one of the markers indicating hemophagocytosis that may have a role in the pathogenesis of Crimean-Congo hemorrhagic fever (CCHF). This study was designed to determine any correlation between serum ferritin and routine diagnostic laboratory markers of CCHF, and to investigate the relationship between serum ferritin levels and disease severity."

"Sixty-six patients with CCHF admitted to the hospital during the spring and summer months of 2006 and 2007 were included in the study. Serum ferritin levels were measured in sera obtained during the initial days of hospitalization. Data from 53 patients showing decreasing platelet counts over the first three days were used for further analysis and these patients were divided into two groups according to disease severity: group A included severe cases with lowest platelet counts $\leq 20 \times 10^9/l$ and group B included mild cases with lowest platelet counts $> 20 \times 10^9/l$. Forty patients (60.6%) were male (mean age 43 ± 17 years). Three patients died, thus the fatality rate was 4.5%. Fifty-one patients (77.3%) had abnormal serum ferritin levels, with levels above 500 ng/ml in 62.1%. There was a significant negative correlation between ferritin levels and concordant platelet counts ($p < 0.001$; $r = -0.416$) and ferritin was also found to be positively correlated with aspartate aminotransferase ($p < 0.001$; $r = 0.625$), alanine aminotransferase ($p < 0.001$; $r = 0.479$), and lactate dehydrogenase ($p < 0.001$; $r = 0.684$). Group A had higher ferritin levels than group B ($p < 0.001$). Receiver operating characteristic analysis revealed that a ferritin level of ≥ 1862 ng/ml had a sensitivity of 87.5% and a specificity of 83.8% in differentiating severe cases from mild ones."

"Increased serum ferritin levels may suggest a significant role of hemophagocytosis in the pathogenesis of CCHF and may be a useful marker for diagnosis, disease activity, and prognosis."

The full article can be found at: (S. Barut, et. al., "Increased serum ferritin levels in patients with Crimean-Congo hemorrhagic fever: can it be a new severity criterion?" International Journal of Infectious Diseases, 2010; 14(1):e50-4). Link not available.

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